This presentation will take approximately one hour to complete.

This presentation is designed for primary care physicians.

Other health care professionals working with patients and their families may also find this program of interest.

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Herpes Simplex Virus Infections in Children

December 8, 2016
Richard D. Andersen, MD
Medical Education and Infectious Disease
Children’s Hospitals and Clinics of Minnesota
Faculty, Department of Pediatrics,
University of Minnesota
Objectives

After completing this course, you will be able to:

• Recognize the usual clinical features of herpes simplex virus infection in newborns, children, and adolescents.
• Discuss diagnostic strategies for identifying HSV infection in newborns and children
• Describe treatment options for various HSV infections
• Discuss pathogenesis of perinatally acquired HSV infection

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BRIEF CASE REVIEW

Baby Girl O. born 2013 in Twin Cities area
Pregnancy complicated by HSV genital infection
Maternal medication: oral acyclovir started 9 days prior to birth
Elective C-section within 3 hours of R.O.M.
Estimated gestational age 35 + weeks
Respiratory difficulty – transfer to Children’s day 7
Ampicillin, cefotaxime and acyclovir begun on admission
2 days later, on maximum ventilatory support, ID consulted
Recommended checking viral studies and serum AST

EMR RESULT:

Serum AST = 17,000 U/L (H)

NEONATAL HSV:
THE 2 KEY TAKE-HOME POINTS

• FEBRILE NEWBORNS IN THE FIRST 7-10 DAYS OF LIFE SHOULD HAVE A SINGLE LIVER FUNCTION TEST AS EARLY MARKER OF OCCULT HSV DISSEMINATION.

• NEWBORNS WITH SUSPECTED NEUROLOGIC INFECTION, ESPECIALLY IN WEEK 2 AND 3 OF LIFE, SHOULD HAVE CSF HSV PCR AND BEGIN ANTIVIRAL THERAPY UNLESS THERE IS CLEAR EVIDENCE OF BACTERIAL INFECTION.

Herpes -- Etymology

• Greek: herpein = to creep
• Latin: serpere = to creep

• 19th Century – “shingles,” herpes zoster, herpes simplex, etc.
• 20th C – type 1, 2 HSV

Virus Shapes and Sizes
Herpesviridae Family and Subfamilies

<table>
<thead>
<tr>
<th>Subfamily</th>
<th>HHV</th>
<th>Description</th>
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<tbody>
<tr>
<td>alpha</td>
<td>1, 2</td>
<td>HSV-1, HSV-2</td>
</tr>
<tr>
<td>alpha</td>
<td>3</td>
<td>VZV</td>
</tr>
<tr>
<td>beta</td>
<td>5</td>
<td>CMV</td>
</tr>
<tr>
<td>beta</td>
<td>6-7</td>
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<td>EBV</td>
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<tr>
<td>gamma</td>
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<td>Kaposi-assoc.</td>
</tr>
</tbody>
</table>

Themes of Herpesviruses

Large size and structural complexity – more opportunities for interruption by antiviral agents?

Latency in specific sites:
- alpha subfamily in neural sites
- beta subfamily in monocytes and T-cells
- gamma subfamily in B-cells

Specific tissue affinities (HSV – mucoepithelial tissue)

Herpes Simplex Virus: Latency and Immunity

- After primary infection, latency is established in the trigeminal (oral HSV) or sacral (genital HSV) ganglia, virus is shed intermittently in secretions
- True immunity appears not to occur, but partial immunity and containment are usual. There is a role of both antibody and cell-mediated immunity in containment
- Some cross-protection between HSV-1 & HSV-2 occurs
- What are the immunologic correlates of containment?

Herpes Simplex Virus: Anatomic Preferences

- HSV-1 has affinity for junctional region of lip
- HSV-2 has affinity for genital area.
- Genital HSV-2 has >>50% rate of recurrence.
- Genital HSV-1 has <<20% rate of recurrence.

Herpesvirus Immune Evasion

1. Herpesviruses tend to establish lifelong infection, partly by evasion of human immune system
2. Most herpesviruses can downregulate MHC-I and MHC-II expression on the cell surface, leading to reduced T-cell activation
3. Cytomegalovirus (CMV) produces a protein functionally nearly identical with IL-10, downregulates TNF-alpha, other pro-inflammatory cytokines

Herpes Simplex Virus: Anatomic Preferences
Herpes Simplex Virus: Epidemiology

• The large majority (>80%) of humans worldwide experience HSV-1 infection and latency.

• A variable minority of humans (15-25%) experience HSV-2 infection and latency. Geographic and socioeconomic factors influence frequency.

• Most neonates (~70%) with HSV-2 infection have no maternal or paternal history of genital HSV infection (silent shedding).

Clinical Spectrum of HSV Infection

Gingivostomatitis – primary oral infection
Primary genital HSV infection
Recurrent oral and genital eruptions
  • Herpes simplex encephalitis (non-neonatal) – sporadic, focal, necrotizing, temporal lobe usually
  • Disseminated HSV in compromised host
  • Herpetic whitlow – finger
  • Eczema herpeticum, herpes gladiatorum – abn. skin
  • Ocular herpes simplex infection

Primary HSV Gingivostomatitis

Primary and Recurrent HSV in Female & Male

Perinatal HSV Transmission

• The large majority of neonatal HSV infections are nataly acquired

• Occasionally congenital HSV infection occurs, often following primary maternal HSV in pregnancy

• Occasionally immediate post-partum HSV transmission occurs, usually following exposure to individual with oral HSV infection
Maternal Status and Neonatal HSV Infection

- **Primary** maternal HSV infection near term (more extensive lesions, fever, adenopathy, etc.) is associated with very high risk (30-50%) of neonatal infection and warrants empiric therapy of newborn. Presumed acquisition by viremic spread.

- **Secondary** or silent maternal HSV infection is associated with a low risk (<3%) of neonatal infection. Maternal shedding at delivery as high as 0.5-1.0%, yet clinical disease in neonate 1:3000 live births.

Patterns of Natally Acquired HSV Infection

- **Skin, eyes, mucous membranes** – variable timing, usually in the first 2 weeks. Diagnosis usually rapid.

- **Disseminated** – usually presents in the first week. May be occult dissemination, only half will have skin lesions. High mortality, especially with absence of skin lesions and with delayed diagnosis.

- **Central Nervous System (+/- skin)** – usually presents with CNS symptoms in the 2nd or 3rd week and is associated with high morbidity.

Primary HSV Pneumonia Following Aspiration at Birth
HSV ENCEPHALITIS

• Unlike neonatal CNS infection with HSV, children and adults usually have focal disease, often temporal lobe.
• HSV PCR on CSF has virtually eliminated brain biopsy for diagnosis.
• Neurologic sequelae are frequent, depend on age and status at diagnosis.

HSV Vesicle

Rapid Diagnosis – The Tzanck Prep

Dr. Arnault Tzanck
The Tzanck Preparation

Natally Acquired HSV – Skin Disease Only

Dr. Arnault Tzanck
The Tzanck Preparation

Natally Acquired HSV – Skin Disease Only
TORCH Titers: Conceptual & Diagnostic Value?

- The term “ToRCH” infection was introduced 40 years ago (Nahmias) to unify evaluation of perinatal infection
- Toxoplasma—Rubella—Cytomegalovirus—Herpes are evaluated in newborns with apparent infection
- Serologic studies are the core of this evaluation

Extinguishing the ToRCH

- “ToRCH titers” distract from the current diagnostic strategies of culture and rapid (FA or PCR) testing
- CMV is common, toxoplasma uncommon (in MN) and rubella rare. All are usually congenital.
- Herpes simplex infection is usually natailly acquired.
- Cultures, FA and PCR testing are essential. “ToRCH infection” is not useful conceptually.

Current Diagnostic Approach to HSV

- Skin lesions – scrape base of vesicle and send for viral culture (suspect HSV) and rapid FA. Result usually < 24 hours.
- Sensitivity of culture/FA system is excellent and specific for HSV-1, HSV-2 (or VZV).
- Cerebrospinal fluid – culture insensitive even in neonate – will miss >70%. Send CSF PCR (Mayo)
- Occasional use ofuffy coat for viral detection.
- Occasional use of serology (retrospective) for HSV

Treatment of Neonatal HSV Infection

- The advent of cancer chemotherapy led to interest in antiviral agents.
- Cytosine arabinoside (Ara-C) trials for HSV found it to be unsatisfactory.
- Prevailing belief that antiviral agents would be too toxic to normal cells to be useful in serious viral disease
- Efficacy with HSV in adults and neonates studied -- vidarabine (Ara-A) vs placebo.

Treatment of HSV: Gertrude Elion

- Entered college age 15 & BS/summa cum laude 19.
- Wished to be a chemist, difficulty finding work, pursued MS in chemistry
- WWII – women >> men, Burroughs-Wellcome company hired her
- Began 40 year research & development collaboration with Dr. George Hitchings

A Remarkable Journey

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- Wished to be a chemist, difficulty finding work, pursued MS in chemistry
- WWII – women >> men, Burroughs-Wellcome company hired her
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Gertrude Elion’s Career
Lab at B-W developed:
6-mercaptopurine
Azathioprine
Trimethoprim/sulfa
Allopurinol
Pyrimethamine
Acyclovir
(Azidothymidine)

Gertrude Elion
- Received Nobel Prize in Medicine in 1988 for her pioneering work in drug development
- First woman to be inducted into the U.S. Inventor’s Hall of Fame
- National Medal of Science awarded by President Bush in 1991

Treatment of Neonatal HSV Infection
- Initial vidarabine vs. placebo study proved efficacy of vidarabine (1970’s)
- Comparative trial of vidarabine vs. acyclovir proved at least equal efficacy and much greater ease of administration (1980’s)
- Acyclovir neonatal dosing has doubled since initial studies, from 30mg/kg/day to 60 mg/kg/day, first with CNS disease, now with all categories.
- Usual course is 21 days for CNS disease and 14 days for other categories.

Prevention of Neonatal HSV Disease
- Reliance on maternal history of HSV?
- Universal or selective serologic screening?
- Treatment of maternal HSV disease in pregnancy?
- Preventive medication in mothers w/ + HSV history?
- Role of Caesarean section to prevent transmission?
- Approach to post-partum mother with cold sore?
- Cautionary comments to all parents re HSV exposure?

C-Section to Prevent Neonatal HSV
- Prevailing strategy in 1980’s: culture weekly late 3rd trimester, base C-section decision on last 2 cultures
- Arvin et al, NEJM, 1986 – studied 434 Bay Area subjects with recurrent genital herpes:
  - Number w/ + cultures ante partum 17/434
  - Number of these w/ + cultures at delivery 0/17
  - Number w/ + cultures at delivery 5/354
  - Number of these w/ + cultures antepartum 0/5

Cost-Benefit of C-Section for HSV (1993)
- C-section for women with only a history of genital HSV results in 1580 excess C-section per poor neonatal outcome.
- $2,500,000 per case averted. Cost and maternal morbidity > neonatal benefit.
- Low cost/morbidity and high neonatal benefit of C-section for women with active lesions at delivery

- **Level B Recommendations (limited or inconsistent scientific evidence):**
  a. Women with active recurrent genital HSV should be offered suppressive therapy at/beyond 36 weeks
  b. Cesarean section is indicated if active genital lesions or prodromal symptoms at delivery

- **Level C Recommendations (consensus or expert opinion):**
  a. In women with P.R.O.M., no consensus on risk/benefit
  b. C-section not recommended w/ no active lesions but + HSV history
  c. Routine ante partum cultures not recommended if asymptomatic
  d. Routine screening of all pregnant women for HSV not recommended

**NEONATAL HSV: THE 2 KEY TAKE-HOME POINTS**

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**Postnatally Acquired HSV with Recurrence: A Management Challenge**

- Maternal postpartum HSV oral reactivation warrants early treatment
- Role for topical acyclovir as adjunct to oral?
- Masking when in contact with neonate is essential until totally inactive
- Mother should be excluded from nursery

**Low-Tech Infection Control: Recurrent Focus Post-Neonatal Infection**

**Maternal Postpartum HSV Reactivation**

- Gestational Age and HSV Replication in Placental Lymphocytes

<table>
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<th>48-72</th>
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<tr>
<td>Term</td>
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Labor and HSV Replication in Placental Lymphocytes

<table>
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<tr>
<td>24-48</td>
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<tr>
<td>48-72</td>
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Disseminated HSV in Neonate: Speculation on Pathogenesis

- Fulminant dissemination of HSV in neonate is relatively restricted to the early days of life.
- Immune deficits related to HSV containment do not abruptly normalize after the early days of life.
- Placental lymphocytes appear to permit significantly enhanced replication after labor compared with C-section placentae.
- Speculation: The physiologic alterations of labor and delivery transiently alter intracellular HSV permissiveness for replication.
- The lymphocyte may serve as “Trojan horse” in dissemination of infection.

Extended Oral Acyclovir Suppression Improves Neurodevelopmental Outcome

- 1990’s – recognition of neurodevelopmental compromise in infants, even in infants believed to have had skin, eye, mucous membrane disease only.
- 2000’s – recognition of reduced cutaneous lesions and excellent tolerance in infants receiving 6-month course of oral acyclovir suppressive therapy.
- 2011 – Kimberlin et al. NEJM;365(14):1284 report clear improvement in neurodevelopmental outcome in national collaborative study, acyclovir vs. placebo.

The Prevention Frontier: HSV Vaccines

- Preventive vs. therapeutic vaccines
- Experience with HPV vaccine suggests the possibility of mucosal impact with injectable vaccine
- Glycoprotein subunit vaccines (esp. glycoprotein D) have been most widely studied. Recent large trial (Herpevac) showed efficacy HSV-1 >> HSV-2.
- Replication defective strains of HSV, e.g. with deletion of gene for glycoprotein D, show promise in increased ADCC

Prevention: Post-Natal Transmission of HSV

TABLOID HEADLINE: Did I kill my baby with a kiss?

“How an anguished mother didn’t discover the danger of the common cold sore virus until it was too late…”

Neonatal HSV: Prevention of Postpartum Acquisition

- Increased risk of HSV reactivation following use of epidural morphine/other medications for C-section?
- Early treatment with acyclovir and physical barrier to transmission of oral HSV lesions from mother.
- General recommendation to all new parents that newborns should not be in contact with people with respiratory illness and cold sores on the lip in the early weeks of life.